PATENT SPECIFICATION

763,301

Date of Application and filing Complete Specification: Sept. 2, 1954.

No. 25511/54.

Application made in Italy on Sept. 5, 1953.

Complete Specification Published: Dec. 12, 1956.

Index at acceptance:—Class 2(3), U4A2, U4C(1:4:5).

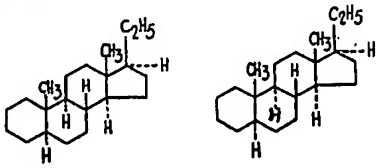
COMPLETE SPECIFICATION

Process for the Reduction of Δ^4-3-Keto-Steroids to 5-β-Dihydro-Steroids

We, FARMACEUTICI ITALIA S.A., a Company incorporated under the laws of Italy, of 18, Via Filippo Turati, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the reduction of the 4(5) double bond of Δ^4-3-keto-steroids by catalytic hydrogenation; as is known, the compounds obtained by such reduction exists in two isomeric forms, named respectively normal or cis- or β-series and allo- or trans- or α-series.

In fact, the perhydrocyclopentenophenanthrene system which forms the fundamental structure of steroids, contains six centres of asymmetry associated with the carbon atoms of the merger of rings A/B, B/C and C/D. All natural steroids, excepting the cardioactive ones, are derived from one or the other of the C—5 isomers, represented, by way of example, by the pregnane (I) and allopregnane (II) formulae



(I) normal or cis- or β-series. (II) allo- or trans- or α-series.

By convention, the configuration is indicated in the formulae by using a solid line for a group which projects above the plane of the nucleus and a dotted line for a group extending below this plane; the first one is called a β configuration and the second an α configuration. Further by convention, the β-configuration is assigned to the methyl group in C—10, as a reference point.

The catalytic hydrogenation of Δ^5-3-hydroxy-steroids yields almost exclusively saturated derivatives of the 5α(allo or trans)-series.

On the other hand, there are examples in the literature of reduction of Δ^4-3-ketones to mixtures of corresponding ketones of the 5-β (normal or cis) and 5-α series.

It is also known that alkalies and acids frequently alter the stereochemical course of a reduction and that alkalies favour a 5-β configuration with the Δ^4-3-ketones of sapogenins.

The alkali influence has been studied also in the 3-keto-Δ^4-steroid series e.g. Δ^4-pregnen-3,20-dione, and a remarkable increase of the amount of 5-β-dihydro isomer formed has been noted when using as alkali KOH in methanol or ethanol solution or when adding an alcoholic solution of KOH to the dioxane solution of the compound to be hydrogenated.

It has now been found, and this forms the object of the present invention, that the use of triethylamine, instead of KOH, in the reduction of Δ^4-3-keto-steroids having a methylene group in the nucleus at the 11-position is considerably more effective than the use of alkali, as regards the orientation of the reaction towards the formation of β-series isomers.

This result is all the more surprising in as much as for triethylamine, though the same is a known promoter for hydrogenating catalysts, the capacity of altering the reduction in a stereochemical direction in steroids having a methylene group in the nucleus at the 11-position, as done by alkalies, is not known.

The invention accordingly provides a process for the reduction of the 4(5) double bond of a Δ^4-3-keto-steroids having a methylene group in the nucleus at the 11-position to form isomeric 5-α- and 5-β- derivatives by means of catalytic hydrogenation with a selective promoter for the formation of the 5-β-isomers, wherein triethylamine is used as the promoter and the catalyst is palladium-carbon containing 5% of palladium.

Preferably, the process in accordance with the present invention is characterized by the fact that the Δ^4-3-keto-steroid to be hydrogenated is dissolved in an inert organic solvent; triethylamine and the hydrogenation catalyst are added and hydrogenation is carried out in the usual manner at room temperature and temperature and pressure in hydrogen atmos-

[Price 3s. 0d.]

phere. As a solvent, an organic, non-reactive, neutral solvent is used which must not be attacked by hydrogen and must not react with triethylamine, such as, for instance, ethanol, ether, ethyl acetate or methylcyclohexane; preferably pure *p*-dioxane is used; and from about 0.3 to 0.7 parts by weight of triethylamine and from about 1 to 3 parts of palladium-carbon catalyst, containing 5% of Pd, for 10 parts of the steroid to be reduced are used.

The reaction velocity, but not the steric direction of the reaction, depends on the triethylamine and palladium proportions. The wanted isomer is isolated from the reaction product by methods known *per se*. The double bond in α,β, in respect of the ketone in C—3 is reduced selectively (without producing attack on other reducible groups eventually present in the molecule) with remarkably higher 5-β-dihydro isomer yields than those obtained by addition of KOH and in a shorter period of time than that necessary to carry out the same reaction without addition of alkali or in the presence of KOH. For example, the reduction of progesterone yields allopregnan-3,20-dione (5α-dihydro) and pregnan-3,20-dione (5β-dihydro) in neutral medium, in a ratio of about 3:1, in the presence of KOH, of 1:1 and in the presence of triethylamine, of 1:4.

It must further be born in mind that in progesterone and its derivatives, under the influence of KOH, an isomerization in C—17 can take place; this hazard does not exist when using triethylamine.

The advantage of obtaining in prevailing amounts derivatives of the 5-β series by reduction of the 3-keto-Δ^4-steroids consists in the fact that it is easy to introduce again from these compounds the double bond into C—4, which is typical for all steroid hormones (e.g. testosterone, progesterone, desoxycorticosterone and cortisone) whereas from compounds of the 5-α series the introduction of the double bond proceeds with extremely low yields.

In this way, for the preparation of cortical steroids of complex structure, recourse can be had to the reduction of the double bond in C—4(5) to protect it during the course of the reaction in which this part of the molecule would be attacked by reagents used to promote conversions in other positions of the steroid, re-introducing it afterwards, when the desired chemical structure has been obtained without a large loss of material.

The hydrogenation method according to the present invention can be applied to the reduction, for example, of testosterone, Δ^4-androstene-3,17-dione or Δ^4-cholestene-3-one.

Some examples are given for illustrating the invention and without restriction.

EXAMPLE 1.

2.0 g. of progesterone (Δ^4-pregnen-3,20-dione) are dissolved in 80 cc. of dioxane, and 1.55 cc. of triethylamine and 0.3 g. of palladium-carbon catalyst containing 5% of Pd are added. Hydrogenation is carried out at room temperature and atmospheric pressure in hydrogen atmosphere. In a period of time of 15—30 minutes one mole of hydrogen is absorbed; the catalyst is filtered off and the solvent and the triethylamine are eliminated by vacuum distillation. The residue is taken up with a little boiling methanol. The scarcely soluble 5-α-dihydroderivative (allopregnan-3,20-dione) formed is filtered off while hot. It weighs 350 mg. and melts at 198—200° C. From the methanol 1.55 g. of 5-β isomer (pregnan-3,20 dione), m.p. 112-118° C., crystallize. The two pure compounds have a m.p. of 200.5° and 123° C., respectively.

EXAMPLE 2.

1.0 g. of desoxycorticosterone acetate, m.p. 155—157° C., dissolved in 50 cc. of dioxane, is hydrogenated, after addition of 0.7 cc. of triethylamine and 300 mg. of palladium carbon catalyst containing 5% of Pd, at room temperature and atmospheric pressure.

After 30 minutes the catalyst is filtered off and the solvent is removed under vacuum. The residue is crystallized from acetone. 310 mg. of 21-acetoxy - allopregnan - 3,20-dione (5-α-isomer), m.p. 193—195° C., and 550 mg. of 21-acetoxy-pregnan-3,20-dione (5-β isomer), m.p. 146—150° C., are obtained.

The same reduction, carried out by A. WETTSTEIN and F. HUNZIKER (Helvetica Chimica Acta, *23*; 764 (1940)) in the absence of triethylamine, has given a 21-acetoxy-allopregnan-dione yield of 12% and a 21-acetoxy-pregnandione yield of 32% (duration time 5 hours).

What we claim is:

1. A process for the reduction of the 4(5) double bond of a Δ^4-3-keto-steroids having a methylene group in the nucleus at the 11-position to form isomeric 5-α- and 5-β-derivatives by means of catalytic hydrogenation with a selective promoter for the formation of the 5-β-isomers, wherein triethylamine is used as the promoter and the catalyst is palladium-carbon containing 5% of palladium.

2. A process as claimed in Claim 1, which comprises dissolving the Δ^4-3-keto-steroid having a methylene group in the nucleus at the 11-position to be hydrogenated in an inert organic solvent, preferably pure *p*-dioxane, adding for 10 parts by weight of steroid, about 0.3 to 0.7 parts by weight of triethylamine and about 1 to 3 parts by weight of palladium-carbon catalyst, containing 5% of palladium, and hydrogenating at room temperature and atmospheric pressure in hydrogen atmosphere.

3. A process as claimed in Claims 1 and 2, when performed substantially as hereinbefore described.

4. The process for the reduction of progesterone to isomeric allopregnan-3,20-dione (5-α-isomer) and pregnan-3,20-dione (5-β-

isomer), substantially as described in the foregoing Example 1.

5. The process for the reduction of desoxycorticosterone acetate to isomeric 21-acetoxyallopregnan-3,20-dione (5-α-isomer) and 21-acetoxy-pregnan-3,20-dione (5-β-isomer) substantially as described in the foregoing Example 2.

6. A 5-β-dihydro-steroid when prepared or produced by the process according to any of Claims 1—3.

7. Pregnan-3,20-dione when prepared or produced by the process particularly described and ascertained in the foregoing Example 1.

8. 21-acetoxy-pregnan - 3,20 - dione, when prepared or produced by the process particularly described and ascertained in the foregoing Example 2.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1956.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.